**SUMMARY OF PITUITARY HORMONE FAMILIES**

Classified by how the cells producing the hormones stain.

**PITUITARY CELL SOURCE** **HORMONE**

ACIDOPHIL GH

PROLACTIN

MODIFIED BASOPHIL MSH

ENDORPHIN

ACTH

BASOPHIL TSH

FSH

LH

NONE (MADE IN HYPOTHALAMUS) OXYTOCIN

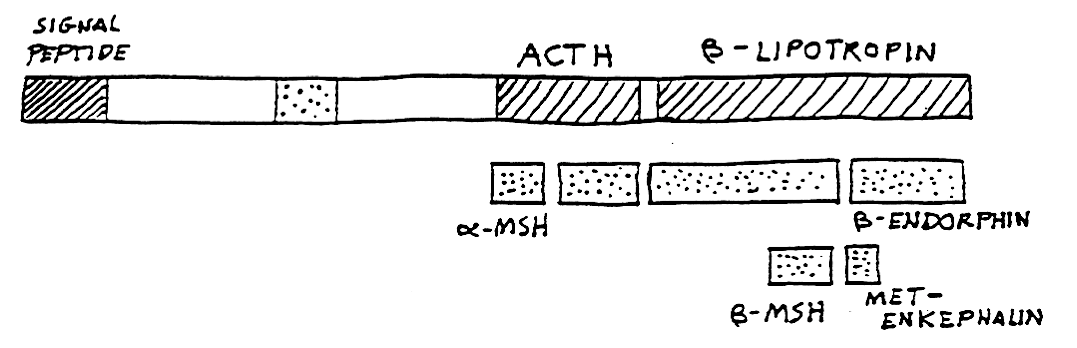
*just stored here* VASOPRESSIN

**NOTES ON ANTERIOR PITUITARY HORMONE FAMILIES**

1. GH and prolactin: are structurally similar, with 84% amino acid homology.
2. MSH, enkaphalin, endorphin, ACTH family: all are derived from same parent molecule, preproopiomelanocortin.
   1. The inactive hormone is proopiomelanocortin
3. TSH, FSH, LH family: are glycoproteins, each with 2 subunits, and the 􏰁 subunit is identical for all 3 hormones (i.e., only the β subunit differs— here's where the AA structure differs.).

**STRUCTURAL RELATIONSHIPS OF THE PROOPIOMELANOCORTIN (POMC) FAMILY**

The entire structure is a preprohormone. At the time it is released from the pituitary gland, it is broken down into various pieces which are the separate hormones shown here.



* Signal Peptide
  + THE PRO-HORMONE with the signal peptide.—pre sequence would be before the signal peptide
* ACTH
* β Lipotropin
  + contains the seq for β-MSH, β-endorphin, and metenkephalin
* MSH
  + 3 different MSH molecules;
    - α-MSH
      * is contained within the ACTH sequence
    - β-MSH
    - γ-MSH
* Endogenous opioids
  + β Endorphin
  + Metenkephalin
  + History of β -endorphin: they were looking for hormones that conserved water in the camel. They looked into the β-lipotropin sequence and they found the link between the body's opiod receptors (known) and that the body actually made endogenous opiods and this led to the discovery of β-endorphin and metenkaphalin as endogenous hormones

**MSH**

1. Active POMC hormones are ACTH, MSH, opioids
2. ACTH and opioids discussed elsewhere in handout
3. MSH
   1. a) Made in pituitary and brain
   2. b) Most MSH-like activity in human due to α-MSH (e.g., pigmentation, appetite,  sexual arousal)—part of the ACTH sequence
   3. c) ACTH-producing tumor 🡪 hyperpigmentation
      1. in Addison's Disease—site specific pigmentation not a tan like a spotchy pigmentation in the axillary area or the mouth. Sometimes pregnant women produce more MSH and can be hyperpigmented.
   4. d) Hypopituitarism🡪pallor
   5. e) 5 receptor types for melanocortin peptides in CNS & periphery
   6. They actually make a MSH-like analogue in Australia that increases sex drive, sexual performance, stimulates erection and in males and females the sexual arousal.

**COMPARISON OF PROLACTIN (PRL) AND GROWTH HORMONE (GH)**

These two hormones have considerable structural similarity and are derived from the same ancestral gene. A brief comparison follows:

1. GH is involved in daily metabolism and prolactin is much more restricted in physiology.
2. Approximate molecular weight of both is 23,000.
3. Pituitary content: GH/PRL ratio is 50/1, and 60% of pituitary cells devoted to GH/PRL (Majority of cells in the anterior pituitary are making GH.)
4. Average plasma levels in male are same for both PRL and GH
5. PRL levels in female are higher because estrogen 🡪 ↑ PRL.
   1. breast production and milk
6. Also, basal GH level and daily secretion in female > male, while tissue sensitivity in male > female.
   1. GH receptor levels in males > female. Tells us that the RECEPTOR is what regulates growth. Men are larger than women!
7. Circulating T1⁄2 is 20-40 min for both PRL and GH.
   1. of both of these hormones
   2. This is the average time for protein derived hormones
8. GH shows high species specificity (e.g., bovine GH will not work in human). PRL is less species specific
   1. Up to 20 years ago, they had to take GH from cadavers only.
   2. Now we know the genes so we can grow it in huge quantities on plasmids of bacteria. Very cheap and easy to grow. Also stimulated a black market for GH.  .
9. GH and PRL receptors similar but not identical blood levels.
10. GH coding gene is on long arm of chromosome 17.

**REGULATION OF PROLACTIN RELEASE**

1. Prolactin doesn't have a 3rd hormone that feeds back
2. Primarily by PRL-releasing hormone (PRH) and prolactin release-inhibiting hormone (PIH)—both from the hypothal.
3. Physiologically significant PRHs include: prolactin-releasing peptide (best candidate), oxytocin, TRH.
   1. TRH-thyrotropin releasing hormones (the one used for releasing TSH from the pituitary
4. PRL is only pituitary hormone that maintains a low tonic release in absence of releasing hormones,  i.e., PIH is the major regulator. 🡪 PIH is DOPAMINE
   1. prolactin is the only pituitary hormone that maintains a low level chronic release --which makes PIH an important regulator
   2. clinical significance--administer DA to control a tumor that releases prolactin. (but you have to administer L-DOPA--b/c this passes through BBB)
5. Dopamine is the primary PIH.
   1. DA is acting as a neurosecretory and not as the NT

**PHYSIOLOGICAL EFFECTS OF PROLACTIN**

1. Stimulation of lactation
2. Potentiation of testosterone effects on prostate
   1. When someone has prostate cancer you must also give this
   2. Also must be considered for prostate cancer treatment.
3. Potentiation of LH effects on Leydig cells of testis
4. **Excess** PRL production results in:
   1. PRL 🡪 ↓ FSH/LH causing…
      1. ↓ Sperm count
         1. The ↓ in FSH/LH b/c of the ↑ PRL inhibits sperm production b/c FSH and LH these are needed for normal spermatogenesis and for female cycle
      2. Amenorrhea
         1. The ↓ in FSH/LH b/c of the ↑ PRL inhibits menses b/c FSH and LH these are needed for normal spermatogenesis and for female cycle
      3. ↓ Libido (both sexes)
         1. Pt may come in w/ ↓ sex drive🡪 If you give them too much L-DOPA to correct this they may come back in w/ hypersex drive
   2. ↑ Anabolism (both sexes) – because PRL has minor GH-like activity
      1. Only when it's in excess bc it's structure is similar to GH so it can produce those effects only when in excess

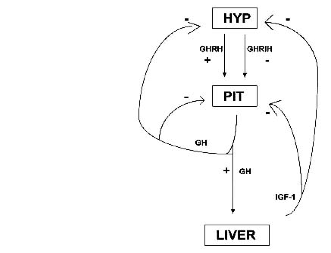
**NON-HORMONAL REGULATION OF GROWTH HORMONE RELEASE**

GH does not have a specific hormone--producing target gland, but it influences a number of body functions, most of which manage to feedback and influence release.

* GH has no real controller in the hormone realm with the exception of IGF1 in the liver which can provide a feedback loop as we'll see later and it's more complex than a simple feedback loop

1. **Factors Which ↑ GH** 
   1. Condition of ↓ in energy substrate—b/c one of the main things GH does is to stimulate metabolism/catabolism, growth of tissues and cell replication, etc so you need energy to produce its effects
      1. Hypoglycemia
      2. Exercise
      3. Fasting
   2. Condition of ↑ circulating amino acids such as arginine
      1. makes sense bc GH stimulates uptake of AA into cells to stimulate growth
      2. Used clinically to test how in tact the GH system is
   3. Stressful stimuli (pyrogens, trauma)
   4. Sleep (initial stage)
      1. In the initial stages of sleep you have GH surge that occurs w/in the first 60-90 minutes of onset of sleep and then in REM sleep it is actually inhibitory to the release of GH
2. **Factors Which ↓ GH** 
   1. Glucose
      1. One action of GH is to stimulate blood glucose so this is a feedback.
   2. Free fatty acids
      1. GH is lipolytic so when you have increase levels of FFA then suppress hormone release
   3. Sleep (REM)
      1. In the initial stages of sleep, there's a GH surge in the first 60-90min of sleep but then when you enter REM sleep it's actually inhibitory to release of GH.

**HORMONAL REGULATION OF GH RELEASE**



1. FEEDBACK LOOP
   1. Strictly hormonal.
   2. Involved GH feeding back and stimulating it own release by influencing by GH releasing hormone (GHRH) and GH release inhibiting hormone (GHRIH—AKA SOMATOSTATIN)
      1. These two regulate at the level of the hypothalamus pituitary connection
   3. GH stimulates the liver to produce IGF-1 so IGF-1 can feed back and inhibit both at the level of the hypothalamus and at the pituitary
2. OTHER HORMONES AFFECT GH RELEASE
   1. Increased by
      1. Vasopressin
         1. ↑ GH release by direct action on the GHRH and GHIRH
         2. acting directly on the neurosecretory cells in the hypothalamus
      2. Glucagon
         1. Used to test GH release. IF you give someone glucagon they should release GH.
      3. Ghrelin
         1. Peptide in the digestive system.
         2. Produced in the stomach and binds to the GH receptors in the pituitary that recognizes the release hormones and release inhibiting hormones.
         3. When it binds it stimulates the release of GH.
         4. It increases appetite and b/c of this and its release of GH It's anticipatory
            1. It increases appetite, there’s going to be food taken in—aka ↑ in energy and ↑ substrate for GH to work so good thing it also stimulates ↑ GH to engage its metabolic effectiveness
   2. Decreased by
      1. Cortisol
         1. It decreases it directly and it also metabolically interacts w/ GH
         2. Prednisone (glucocorticoid) that is chronically given (especially in children) will affect GH function in children and can stunt their growth B/c GH is inhibited by cortisol

**TESTS FOR GH NORMALCY**

1. In normal adults GH too low to measure (So you look at other things to test for it), so need to apply challenge tests to check for deficiency. These include:
   1. **response to exercise \***
   2. **injection of L-DOPA** \*
   3. blood sample 90 min into sleep
   4. response to insulin-induced hypoglycemia
   5. injection of arginine

\*= best ways

1. To assess GH excess:
   1. give glucose to suppress GH
      1. If you don't get a suppression of GH with glucose then there's a problem
   2. measure plasma IGF-1 level
      1. You can measure this in the blood.
      2. This is released in response to GH—So if GH is elevated, you'd expect IGF-1 to be elevated

**PHYSIOLOGICAL EFFECTS OF GROWTH HORMONE**

* **WHAT DOES GH DO TO STIMULATE GROWTH?**
  + Metabolic Level
    - Increases protein synthesis & uptake of AA
    - Preferential use of fats
      * To spare amino acids for use in protein synthesis
        + by mobilizing body fat – ↑ in FFA
        + by limiting glucose use (by antagonizing insulin action)

ensuring that there will be enough glucose in the blood to make sure it has the glucose that it needs to do its job.

Due to a low insulin receptor density in the brain, the main means by which the brain can obtain glucose is by the concentration gradient. You want a high enough glucose amount to ensure that it gets into the brain.

* + - Limiting glucose uptake (insures sufficient glucose in blood for brain use)
  + Cell/Tissue Levels
    - Maturation of cells
    - Cell replication, thereby increasing tissue size –active actions of GH
* **TISSUE GROWTH AND MAINTENANCE**
  + Examples of growth effect:
    - Stimulates cartilage replication and bone formation
    - Stimulates growth of kidney
      * that occurs in childhood and adolescence
  + Example of maintenance effect:
    - Necessary for normal filtration and tubular secretion in kidney (i.e., permissive action of GH)
  + Long-term growth requires GH action on both metabolism and growth
* **REGULATOR OF INTERMEDIARY METABOLISM** 
  + **Anabolic and electrolyte action** - ↑ protein synthesis, primarily via ↑ amino acid transport into cells
    - \*MOST IMPORTANT FUNCTION
  + **Fat metabolism** - general fat mobilization and breakdown, both directly and by countering insulin actions because insulin stores fat!
    - insulin is a totally anabolic hormone and it will tend to store fat
  + **Carbohydrate metabolism** -↑ blood glucose (“diabetogenic action”)
    - Note that GH has both **insulin-like** and **anti-insulin** actions to help manage blood glucose.
      * Insulin-like action: It sensitizes pancreatic insulin-producing cells to glucose
      * Anti-insulin like action: antagonizing the peripheral action of insulin (limits glucose uptake).
    - Thus, provides overall ↑ blood glucose to feed brain, but limits glucose impact in periphery.
    - Is it paradoxical? Actually, no. GH present ensures enough glucose in the blood for peripheral intake. Secondly, it ensures that there is enough insulin to limit excessive glucose so that things still work alright for appropriate homeostasis.
* **SUBCLASSIFICATION OF GROWTH HORMONE EFFECTS** 
  + DIRECT - GH acts **directly** on target cells in its metabolic actions
  + INDIRECT - GH acts **indirectly**, through growth factors that it stimulates, in causing tissue  growth and cell proliferation
    - Example of a growth factor is Insulin-like Growth Factor 1 (IGF-1)
* **CYTOKINES**
  + Family of proteins involved in mediation of immune responses, cellular growth and endocrine function
  + Functional Categories of Cytokines
    - Inflammatory ex: TNFα
    - Immunomodulatory ex: Interferons
    - Chemokines ex: oncostatin M
    - Growth Factors ex: IGF-1, EGF 🡨These are the ones we're going to look at today :)
  + Action is often paracrine or autocrine, but also endocrine
    - IGF-1 actually acts through the blood
  + Some cytokines (e.g., IL-1, IL-6, TNFα) influence production and actions of hormones (e.g., CRH, TRH, cortisol, estradiol, thyroxine) and are themselves influenced by hormones
* **SPECIFIC GROWTH FACTORS**
  + **IGF-I**
    - The most studied growth factor
    - Mediates tissue-growth effect of GH
    - Structurally similar to proinsulin
    - Synthesized in liver, but also locally by many cell types, where it acts locally (autocrine)
    - Acts on all stages of development and growth, including DNA synthesis, mitosis, metabolism
    - There is an IGF-2, but acts primarily on the fetus
    - Mediation of IGF-1 action is multifaceted and complex
      * By an IGF receptor family
      * By IGF binding protein (IGFBP) family
      * IGF binding-protein proteases (regulate availability of IGFBPs)
      * \*\*lots of sites where IGF-1 can be regulated
* **OTHER GROWTH-FACTOR FAMILIES**
  + Usually specific for a given cell type or function
    - Epidermal Growth Factors (EGF)
    - Nerve Growth Factor
    - Vascular-epithelial GF (VEGF)
    - Platelet-derived GF
    - Erythropoietin (EPO)—this is capable of acting as a growth factor on its own w/ or w/o the interactions w/ GH and IGF-1
    - Interferon
    - Transforming GFs

**GH AND ONTOGENY**

* Overall growth is determined by genetics, nutrition and hormones.
  + These 3 factors determine how an individual grows.
* GH most important in infant/child
  + Blood levels of GH in infant/child are higher than in adult
  + Tissue sensitivity (receptor competency) of infant/child greater than in adult
* Further GH increase associated with adolescent growth spurt
  + Reproductive hormone increase and GH increase causes growth spurt
* Tissue sensitivity (receptor competency) in male > female
  + This is why we see differences in male vs. female size, height and weight
* GH levels decrease with aging (as well as receptor competency)
  + Starting around age 50s tissues start to deteriorate and the ↓ in GH and the GH receptor competency with age partially describes why tissues don't work as well
* IGF-1 levels parallel GH levels through life
  + GH produces IGF-1 so follows nicely with the ↓ in GH
* \*\*If you look at a person's final height and weight, it's partially genetically determined. The genetics can dictate how good the receptor competency is for GH, or average release of GH in a day, etc. Translated into action by the GH and the receptor concentrations for it—so final height determined by GH secretory capacity and GH receptor levels
* Other growth - promoting hormones
  + Thyroid
  + Cortisol
  + Testosterone
  + Estradiol
  + Growth-factor families

**DISORDERS OF GH HOMEOSTASIS**

* **Excess** (most common cause of excess if a slow growing pituitary tumor)
  + **Gigantism**
    - excess of GH In childhood
    - Childhood onset
    - Will see excess growth of the long bones
    - Rare
      * Showed a picture of identical twin brothers but one had childhood onset of the excess GH (this brother is way bigger w/ bigger hands and feet)
  + **Acromegaly**
    - Adult onset—More common
    - A common cause of GH excess is a slow-growing pituitary tumor
  + Effects include:
    - Excess long bone growth if childhood onset
    - Excess flat bone and joint growth if adult onset
      * so joints will be very large and bone in places like the jaw will increase in size; the pelvis will be large
    - Excess soft tissue and viscera growth
    - Thick skin, big tongue
    - Decreased subcutaneous fat—makes sense b/c GH is lipolytic
    - Glucose intolerance or diabetes—expected due to glucose homeostasis
    - Increased atherosclerosis
  + Treatment
    - In patients w/ GH excess Injection of long acting somatostatin (GHIRH) can ameliorate symptoms but it doesn't always work it depends on the individual
* **Deficiency** 
  + Childhood onset – **Dwarfism** (> 50 genetic base types) --- They may change the name to be less derogative "little people” or “persons of short stature”
    - Most have genetic basis, some due to pituitary deficiency
    - May have normal proportions or may have short limbs with head over-proportional to torso
    - By definition, must be >3 standard deviations below average height 🡪 person would be about 4’10”
    - These people usually have normal physiology otherwise
    - Effects include:
      * Reduced growth rate
      * Short stature
      * Delayed puberty
      * Delayed bone maturation
      * Moderate obesity –b/c abnormal ability to mobilize fat due to ↓ GH
    - Treatment—Most are correctable by giving GH but some are not.
  + Adult onset - Primarily metabolic effects
* **Insensitivity** 
  + **Laron Syndrome**
    - Genetic receptor deficiency🡪 GH insensitivity
    - Increased GH and decreased IGF-1 b/c no receptors in the liver to allow for production of IGF-1 and allow GH to work
    - Some cases respond to IGF-1 treatment

|  |  |
| --- | --- |
| β **-ENDORPHIN** | |
| **STRUCTURE** | 31 amino acids, is part of β -lipotropin.  β -Lipotropin and ACTH are part of the same precursor, pre-proopiomelanocortin (pre sequence is cleaved before release occurs and then the internal cleavages of proopiomelanocortin to release ACTH, β-endorphin, MSH, etc. occur w/in a cell and can occur selectively) |
| **LOCATION** | Primarily adenohypophysis (anterior pituitary), also periaqueductal gray matter in brain  it surrounds the ventricular system in the brain |
| **GENERAL ROLE** | Involved in behavioral homeostasis (via 5 opioid receptor types—primarily my and epsilon), influencing mood and emotion; mediating these effects by acting as neurotransmitter or as neuromodulator at dendritic terminals. In general, it limits neuron firing by causing **hyperpolarization** (often GABA neurons). Acts via mu and epsilon opioid receptors |
| **SPECIFIC EFFECTS** | * Analgesia 15-30 min duration * Tranquilization 30-60 min duration * Euphoria--↑ sense of well being * ↑ Short-term memory * Large dose causes rigid catatonia * Also causes confusion in some patients who take it |
| **SOME CONDITIONS ASSOCIATED WITH ↑ ENDORPHINS** | * Vigorous exercise -- "the runner's high"   + causes a temporary ↑ in release of endorphins (20 minutes vigorously) you feel pretty good while exercising 80% of people who vigorously exercise experience this but 20% do not ☹ * Intense pain   + causes a fairly large release of endorphins.   + 2 of the most common times are during post-surgery recovery and after burns—so much endorphin release that it may cause some analgesic effects. * Nicotine   + Maybe this helps cause addiction * Deep relaxation   + Yoga w/ biofeedback, etc.   + Mechanisms for release are not well understood. |
| **SOME CONDITIONS ASSOCIATED WITH ↓ ENDORPHINS** | * Depression   + ↓ in endorphins🡪 Unoccupied opioid receptors does not feel good. * Rheumatoid arthritis   + Unusual consideration. They do have a lot of pain but they don't actually increase the release of endorphins.   + Abnormal feedback on the adrenal pituitary feedback is suggested for depression and RA. * Some types of infertility   + ↓ endorphin🡪 ↑ GABA🡪 ↓ GnRH🡪 no ovulation * Some types of cancer   + Relationship between cytokines and endorphin production. |

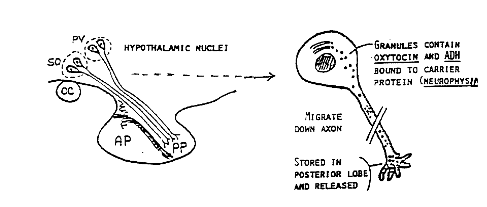
* β-endorphin was discovered by studying high conservations of water in camels

**ENDORPHINS INVOLVED IN MOTIVATION/REWARD:**

* The 2 major agents:
  + β-endorphin—hyperpolarizes GABA neurons (GABA is an important inhibitory NT)
  + Dopamine
* CURRENT THEORY: There are **dopaminergic projections** from brain ventral tegmental area (VTA) to  nucleus accumbens (a pleasure center in the limbic system). **β-endorphin facilitates** dopamine release from VTA by hyperpolarizing GABA neurons, thereby removing inhibition of dopamine neurons (↑ DA In the nucleus accumbens)🡪 sense of pleasure/reward
* Role in infertility
  + ↓ endorphin🡪 ↑ GABA🡪 ↓ GnRH🡪 no ovulation
* Role in reward system
  + ↑ endorphin🡪 ↓ GABA🡪 ↑ DA from VTA🡪 ↑ nucleus accumbens activity

**POSTERIOR PITUITARY (NEUROHYPOPHYSIAL) HORMONES**

* PRODUCTION, TRANSPORT, STORAGE



* + - The granules in the neurosecretory cell body contain oxytocin and ADH bound to carrier protein (Neurophysin)
    - These migrate down the axon and are stored in the posterior pituitary and are released from there.
* SUMMARY
  + Oxytocin and vasopressin (antidiuretic hormone, ADH) are nonapeptides (approx. 1,100 M.W.).
    - Differ in structure only at positions 3 and 8.
  + Synthesized in the neurosecretory-cells of the paraventricular and supraoptic nuclear areas of the hypothalamus.
    - Paraventricular nucleus—oxytocin
    - Supraoptic nucleus—vasopressin (ADH)
  + They both have the same carrier protein🡪 Attach to **neurophysin** carrier protein for transport down the axons to the posterior pituitary, where they are stored or released by exocytosis
    - The neurophysin-hormone complex is considered a **preprohormone**
    - When release occurs the hormone granules break down and most of the neurophysin is cleaved so the hormones enter the blood as active hormones (oxytocin or ADH)
* METABOLISM
  + Hormone granules degraded when released into blood (some neurophysin released, but no no biological activity)
  + Hormone transported as mixture of free and bound (loosely, to albumin)
    - no specific binding proteins for either
  + T1⁄2 is <3min
    - short half life.. not bound to anything or protected from anything
  + Liver and kidney are sites of removal
  + ADH also inactivated in blood
    - oxytocin not degraded in the peripheral circulation but ADH does
    - ADH inactivation in the blood is not a major source of inactivation—most ADH gets where it needs to go
* PRIMARY PHYSIOLOGICAL ACTIONS
  + **Vasopressin (ADH)**
    - Increased renal water absorption (primarily via **medullary collecting ducts**)
    - Proximal tubule is major water reabsorption site, but not vasopressin-controlled
    - Behavioral effects of ADH
      * Stimulates mate tending (male) and maternal behavior (female) in some mammals
        + Some species in which mate tending is carried out by the male not by the female
      * Stimulates sexual motivation in males & females—slightly different than libido. Basically translates to thinking about sex.
  + **Oxytocin** 
    - Contraction of myoepithelial cells in mammary gland (lactation and milk ejection from the breast)
    - Contraction of uterine smooth muscle—important role in parturition (act of giving birth)
    - Behavioral effects
      * ↑ maternal/infant bonding
        + so breast feeding is very good for mother/child
        + Some evidence that it increases bonding between adults as well.
      * Moderates anxiety
        + You decrease anxiety
        + Has been used in the treatment of autism.
* REGULATION OF VASOPRESSIN AND OXYTOCIN RELEASE
  + Vasopressin
    - Mainly regulated by plasma osmolality
    - Blood volume and pressure can also influence via
      * neural paths from baro- and volume receptors (heart/aorta/carotid sinus) to CNS neurosecretory (ADH) cells
      * volume/pressure effects on CNS thresholds for ADH release —it alters the threshold for release
  + Oxytocin released primarily by
    - Suckling reflex: direct neural connections from nipple to hypothalamus
      * Stimulates release of oxytocin so ensures that there is an ejection of milk.
    - Cervical stimulation (coitus= intercourse or parturition=act of giving birth) to the hypothalamus: neural connections from cervix to hypothalamus
      * Milk can be ejected during sexual encounters due to this
      * Very important for parturition

**FLUID BALANCE DISORDERS**

* ADH deficiency (diabetes insipidus)
  + Symptoms
    - Dilute urine
    - ↑ Urination frequency
    - Increased thirst—it can reach the point where the pt only drinks and pees!
  + Treatment
    - **Desmopressin** 
      * Binds to renal V2 receptors in the collecting ducts which stimulates water reabsorption
      * Acts as vasopressin analogue
* Syndrome of Inappropriate ADH (SIADH)—TOO MUCH ADH RELEASE
  + Symptoms
    - Normal renal/adrenal function
    - Hyponatremia
      * low levels of Na in the blood but you're still excreting ADH
    - Continued renal Na+ excretion
    - No clinical volume depletion
    - Increased urine osmolality
  + Treatment
    - Limit fluid intake
    - Give hypertonic saline (↑ plasma osmolality)
    - For long term give
      * **Naloxone** to ↓ vasopressin release
      * **Demeclocycline** to block vasopressin action in kidney